

New EMPIR project – Metrology for Drug Delivery

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Abstract

This document presents the scientific and technical objectives, state of the art and expected progress beyond it, and most importantly the expected impact on metrology, science, standards, and society of the new joint research project - MeDD II, Metrology for drug delivery (follow up of project MeDD I). It was selected for funding through the EURAMET EMPIR program of the European Commission and the participating countries. The project starts in June 2019 and will last for three years. It involves 15 partners from National and Designated Metrology Institutes, companies, and academia. The main objective is to enable traceable measurements of volume, flow and pressure of existing drug delivery devices (for example infusion pumps and analysers) and inline sensors that work at flow rates lower than 100 nL/min, in order to prevent inaccurate measurement results. This project will also investigate fast changing flow rates, liquid mixing behaviour and occlusion phenomena in multi-infusion systems with the purpose of improving dosing accuracy in each infusion line.

1. Introduction

The most commonly used form of therapy in hospital environment is infusion therapy [1], which implies that drug delivery is a critical aspect in health safety. Because of the widespread application by many users in critical health situations, infusion errors are often made, with potential dramatic effects in the patients. There are various examples where adverse incidents, morbidity and even mortality, can be traced back to poor drug delivery. The authors Snijder et al [2] published a review in which medical errors associated with flow rate variability in infusion devices are described, where they emphasized the severe and lasting health damage that has occurred.

A well-defined metrological infrastructure is needed to allow infusion pump manufacturers to include robust information on the “real” dose delivered to the patient, and drug delivery devices operators to have a better metrological knowledge of these critical devices, thus preventing incorrect measurement results and significantly improving patient safety.

Metrology can bridge the knowledge gap by designing a representative multi-infusion intravenous system for testing how different liquids mix and how this affects drugs concentrations. The increasing implementations of novel microfluidic solutions in healthcare urge the

development of a metrological infrastructure for validating quality and reproducibility [3].

The new Joint Research Project - MeDD II, Metrology for drug delivery funded under the EMPIR program of the European Commission starts in June 2019, will last for three years involving 15 partners, including: 9 National and Designated Metrology Institutes (IPQ-Portugal, LNE-CETIAT - France, CMI – Chez Republic, DTI - Denmark, METAS - Switzerland, NEL – United Kingdom, NQIS - Greece, RISE – Sweden and KRIS - Korea), 4 companies (DNV GL – The Netherlands, HSG-IMIT - Germany, INESC MN - Portugal, BHT – The Netherlands) and 2 University Hospitals (THL - Germany, UMCU – The Netherlands). This project is coordinated by IPQ, the Portuguese Institute of Quality and has the overall objective to improve dosing accuracy and enable traceable measurements of volume, flow and pressure of existing drug delivery devices and inline sensors operating at very low flow rates (lower than 100 nL/min). This can be achieved through the development of new calibration methods and improved metrological infrastructures. Another goal of this project is to investigate the influence of: different flow rate regimes; physical properties of the infused fluids (e.g., viscoelasticity); and occlusion phenomena in multi-infusion systems. This knowledge will help

preventing inaccurate measurement results and thus improve patient safety.

2. State of the art and progress beyond it

In 2004, in a metrological effort to understand and improve multi-infusion, Clark [4] defined the crucial performance aspect of an infusion system and established the importance of a patient receiving the correct dose, of the required substances, in a certain time. However, in multi-infusion, this is not an easy task. The first steps towards a better understanding of the real flow rates and of the drugs' concentration delivered to the patient were made in 2 previous projects [5, 6]. In MeDD I (Metrology for Drug Delivery I) [5] the aim was to prevent errors by upgrading calibration services and improving knowledge transfer to the end-user [5]. An infrastructure, consisting of traceable calibration services for drug delivery systems for flow rates down to 100 nL/min, was developed in five European National Metrology Institutes (NMIs) [7, 8]. Syringe pumps and peristaltic pumps with accessories were tested [9]. Additionally, the effects of variations in several physical parameters in infusion systems were incorporated in a predictive model [10].

This new project will go beyond the research conducted during the project MeDD I [5] by investigating the influence of fast changing flow rates due to a change in the pre-set flow rate. Also, a multi-infusion setup will be developed to investigate fluid flow rates and fluid compositions in the outlet of the infusion line. This setup will allow the assessment of the performance of drug delivery devices in multi-infusion systems and the determination of the concentration of each drug being administered.

3. Scientific Objectives

The overall goal is to enable traceable measurements of volume, flow and pressure of existing drug delivery devices and inline sensors that work at a flow rate lower than 100 nL/min. This project will also investigate different flow rate regimes, liquid mixing behaviour and occlusion phenomena in multi-infusion systems with the purpose of improving dosing accuracy in each infusion line.

The specific objectives of the project are:

1. To develop new traceable techniques for generating and measuring the response time or delay time against changes in flow rate, in the interval from 5 nL/min to 100 nL/min, using Newtonian liquids, for example, optical methods.
2. To upgrade the existing flow facilities and knowledge of the participant NMIs in order to enable traceable inline measurement of the dynamic viscosity of Newtonian liquids, as a function of the flow rate and pressure drop, with a target relative uncertainty of 2 % ($k=2$).

3. To develop and validate novel calibration procedures for existing drug delivery devices traceable to a primary standard and a target relative uncertainty of 2 % for a range of 5 nL/min up to 600 mL/min. In addition, to develop a proof-of-concept of an on-chip microfluidic pump used as transfer standard in drug discovery and organ-on-a-chip applications in the flow rates from 5 nL/min to 100 nL/min.

4. To design and develop a multi infusion system containing check valves, with several options for testing the miscibility of liquids (with different viscosities and flow rates) and how this affects drugs' concentration.

5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain, (i.e. accredited laboratories, instrumentation manufacturers, etc.), standards developing organizations and end-users (i.e. hospitals and health centres).

4. Impact

4.1 On society and health sectors

The main goal of this project is to improve diagnostics, patient treatment and patient safety by developing new calibration methods, resulting in an adequate traceability chain for flow rate measurements performed by several drug delivery devices such as multi infusion systems, insulin pumps and pain controllers working at flow rates as low as 5 nL/min. It is known that drug errors account for a significant percentage of medical errors, with dosing errors being a significant subset of them [11-14]. Depending on the drug type, the patient characteristics and the applied therapy, dosing errors can have severe consequences, including a substantial number of fatalities.

A better understanding on how dosing errors may occur, and how to increase the accuracy of the drug delivery devices will have a noticeable impact on the health industry and significantly improve patient treatment and safety. Therefore, any attempt to prevent adverse events by improving the knowledge on actual doses can already make an enormous difference for the individual patient, especially newborn babies, and have a significant impact on the health sector as a whole. A considerable impact on society through improved patient safety can be expected by improving the calibration and administration conditions for drug delivery devices and setups. Important examples can be found in chemotherapy, in anaesthesia, in the operating theatre and in nursery wards, especially for the neonates. The calibration methods are also important in drug injection applications in very small anatomic regions of the body, for example in the inner ear. Improving metrology for microfluidic methods in this field could help to find new horizons for the treatment of acute deafness and Meniere's disease.

Furthermore, occlusion alarms' quality can be improved, and occlusion alarm fatigue diminished by more reliable pressure measurements.

Accurate drug delivery will also have economic benefits. In modern medicine, many sophisticated pharmaceuticals are available, but only at high prices. Metrology can help prevent waste of expensive medication, by enabling the delivery of accurate dosage.

Finally, the infusion pumps analysers used by the hospitals' maintenance to calibrate the in-house used infusion devices need to be calibrated against a reference. However, in most of the cases the traceability of the these devices is only guarantee in hospitals with ISO 9001 certification since it is mandatory.

4.2 On metrology

This project will upgrade various existing facilities for flow measurements from 5 nL/min up to 100 nL/min using different Newtonian fluids as test medium. These new facilities will be validated by means of an inter-comparison with stable transfer standards allowing the recognition of new measurement capabilities.

New calibration methods will be developed based on optical methods and this knowledge will be disseminated across the scientific community by relevant publications in scientific journals and congresses.

These new calibration methods will be beneficial for both accredited laboratories and manufacturers of drug delivery devices. These new procedures can later be updated for microfluidic devices used in health, mainly in organ-on-a-chip technology. A calibration guide for the different type of drug delivery devices will be drafted describing the calibration methods, conditions under which they are to be operated, target uncertainty and best working practices. The draft will be submitted to EURAMET and made available to end users.

4.3 On standardisation

In this project, procedures and methods for the calibration of drug delivery devices already on the market are going to be developed. This information will be supplied to the relevant ISO technical committees (TC). For example, the current version of IEC 60601-2-24 used by manufacturers to develop drug delivery devices and by laboratories and maintenance departments of hospitals to verify and calibrate drug delivery devices, is roughly 20 years old and is outdated. Moreover, the given measurement methods are not suitable for very low flow rates (< 100 nL/min) relevant to implantable infusion pumps where applications are encountered. An urging need to update the measurement procedures for different types of pumps and master calibrators is widely accepted. It is envisaged that the project will impact on Section Eight of IEC 60601-2-24 (Accuracy of operating data and protection against hazardous output).

This project can also supply inputs on the Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices that are currently lacking information regarding maximum

permissible errors of several medical devices, including drug delivery devices.

5. Conclusion

By improving the flow rate measurements accuracy of drug delivery devices, dosing errors will be reduced, and lives will be saved. This can be achieved by wider uptake of traceable calibrations of low and ultra-low flow infusion (master) devices and by improved knowledge of calibrating drug delivery devices in clinical environments, especially in the case of multiple infusion systems. This project directly benefits the general community because it allows identifying and reducing dosing errors in drug delivery devices used for patient treatment and diagnostic.

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